

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JULY 8, 2004

VOL. 351 NO. 2

Preoperative PSA Velocity and the Risk of Death from Prostate Cancer after Radical Prostatectomy

Anthony V. D'Amico, M.D., Ph.D., Ming-Hui Chen, Ph.D., Kimberly A. Roehl, M.P.H., and William J. Catalona, M.D.

ABSTRACT

BACKGROUND

We evaluated whether men at risk for death from prostate cancer after radical prostatectomy can be identified using information available at diagnosis.

METHODS

We studied 1095 men with localized prostate cancer to assess whether the rate of rise in the prostate-specific antigen (PSA) level — the PSA velocity — during the year before diagnosis, the PSA level at diagnosis, the Gleason score, and the clinical tumor stage could predict the time to death from prostate cancer and death from any cause after radical prostatectomy.

RESULTS

As compared with an annual PSA velocity of 2.0 ng per milliliter or less, an annual PSA velocity of more than 2.0 ng per milliliter was associated with a significantly shorter time to death from prostate cancer ($P < 0.001$) and death from any cause ($P = 0.01$). An increasing PSA level at diagnosis ($P = 0.01$), a Gleason score of 8, 9, or 10 ($P = 0.02$), and a clinical tumor stage of T2 ($P < 0.001$) also predicted the time to death from prostate cancer. For men with an annual PSA velocity of more than 2.0 ng per milliliter, estimates of the risk of death from prostate cancer and death from any cause seven years after radical prostatectomy were also influenced by the PSA level, tumor stage, and Gleason score at diagnosis.

CONCLUSIONS

Men whose PSA level increases by more than 2.0 ng per milliliter during the year before the diagnosis of prostate cancer may have a relatively high risk of death from prostate cancer despite undergoing radical prostatectomy.

From Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston (A.V.D.); the Department of Radiation Oncology, Harvard Medical School, Boston (A.V.D.); the Department of Statistics, University of Connecticut, Storrs (M.-H.C.); the Department of Psychiatry, Washington University School of Medicine, St. Louis (K.A.R.); and the Department of Urology, Northwestern Feinberg School of Medicine, Chicago (W.J.C.). Address reprint requests to Dr. D'Amico at the Department of Radiation Oncology L-2 Level, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at adamico@lroc.harvard.edu.

N Engl J Med 2004;351:125-35.

Copyright © 2004 Massachusetts Medical Society.

WATCHFUL WAITING IS AN OPTION for managing localized prostate cancer when both the patient and the physician agree that the potential adverse effects of treatment exceed the expected benefit.¹ To date, the results of a single randomized trial in which watchful waiting was compared with radical prostatectomy have been reported.² In that study, begun before screening with the use of prostate-specific antigen (PSA) measurements became widespread, the median age was 64.7 years, and 12 percent of men had a tumor (T) stage of T1b, 12 percent T1c, and 76 percent T2 (a palpable localized mass in the prostate). There was no significant difference in overall survival between the two groups, but estimates of death from prostate cancer were significantly higher in the watchful waiting group.

Today, the vast majority of men with prostate cancer present with a nonpalpable tumor (stage T1c) and come to medical attention because of an elevated or rising level of PSA.³ Additional evidence is therefore needed to guide management in the era of PSA screening. Such evidence is embodied in a randomized trial⁴ comparing radical prostatectomy with watchful waiting that includes men in whom prostate cancer was diagnosed during the era of PSA screening, but data from this trial will not be analyzed for several years. Ways of identifying men who are unlikely to be cured of prostate cancer despite radical prostatectomy could aid in making decisions about treatment in such men.

Several studies⁵⁻⁷ have found that, when considered alone, the rate of rise in PSA levels — the PSA velocity — before the diagnosis of prostate cancer can predict tumor stage, grade, and in one study, the time to disease recurrence, as defined by the PSA level after radical prostatectomy.⁷ However, not all men with a recurrence die of prostate cancer,⁸ because competing causes of mortality are frequent, especially in cases of prostate cancer with a protracted course. We assessed whether the PSA velocity during the year before the diagnosis of prostate cancer, the PSA level at diagnosis, the Gleason score, and the tumor stage can identify men at risk for death from prostate cancer and death from any cause after radical prostatectomy.

METHODS

PATIENT SELECTION AND TREATMENT

Pretreatment and follow-up information were compiled on 1804 men who participated in a prospective prostate-cancer screening study and were treated

with radical prostatectomy at Barnes-Jewish Hospital in St. Louis from January 1, 1989, to June 1, 2002, for stage T1c or T2 prostate cancer. Twelve men were found to have lymph-node metastases at the time of the final pathological evaluation, despite the absence of noted lymph-node involvement intraoperatively. These 12 men had an undetectable PSA level at the first postoperative evaluation and were not treated with adjuvant hormonal therapy, and were therefore included in the study. A total of 689 men who had only a single measurement of PSA preoperatively were excluded from the study, as were 20 men who had received adjuvant radiotherapy. The remaining 1095 men comprised the study cohort. No patient received adjuvant hormonal therapy. Each man provided written informed consent before study entry; the study was approved by the institutional review board. The median age of the men at the time of initial therapy was 65.4 years (range, 43.3 to 83.5). Seventy-one percent of men had stage T1c, and 95 percent had a PSA level of 10.0 ng per milliliter or less. The median PSA level was 4.3 ng per milliliter (range, 0.3 to 58.2). Table 1 shows the clinical characteristics of the men before treatment.

STAGING

The preoperative workup included a digital rectal examination, measurement of serum PSA, and a transrectal needle biopsy of the prostate. The biopsy was performed under ultrasonographic guidance, usually with the use of an 18-gauge Tru-Cut needle (Travenol Laboratories), and at least six cores obtained for all men whose PSA level exceeded 2.5 ng per milliliter, according to the rules of the screening-study protocol. Among the men with a PSA velocity of more than 2.0 ng per milliliter per year, 143, 65, and 54 received a diagnosis of prostate cancer after one, two, or three or more sets of prostate biopsies, respectively. A genitourinary pathologist at Barnes-Jewish Hospital assigned the Gleason score⁹ for all biopsy and prostatectomy specimens. The clinical tumor stage was based on the results of the digital rectal examination (and not on radiologic or biopsy information) with the use of the 2002 American Joint Commission on Cancer (AJCC) staging system.¹⁰ The pathological tumor stage was determined with the use of the 1992 AJCC staging system to permit a distinction between unilateral and bilateral extracapsular extension.¹¹ A bone scan was obtained within three months before radical prostatectomy, and the result was negative in all men.

Before May 2000, an enzyme immunoassay (Tan-

Table 1. Clinical Characteristics of the 1095 Men before Treatment.*

Characteristic	No. (%)
Preoperative PSA	
≤4.0 ng/ml	466 (43)
>4.0–10.0 ng/ml	570 (52)
10.1–20.0 ng/ml	42 (4)
>20.0 ng/ml	17 (2)
Gleason score of biopsy specimen	
≤6	916 (84)
7	133 (12)
8–10	46 (4)
Clinical tumor stage†	
1c	779 (71)
2a	267 (24)
2b	45 (4)
2c	4 (<1)
Age at the time of radical prostatectomy	
<50 yr	5 (<1)
50–59 yr	222 (20)
60–69 yr	615 (56)
≥70 yr	253 (23)

* Because of rounding, percentages may not sum to 100.
 † The categories are those of the American Joint Commission on Cancer.

dem-E PSA, Hybritech) was used to measure PSA preoperatively. Beginning in May 2000, the chemiluminescence method was used with the Access Analyzer (Beckman Coulter) and PSA antibody (Hybritech), after confirmation that this approach yielded equivalent results. The PSA level was measured and digital rectal examination performed at intervals of 6 to 12 months before and again just before diagnosis, and all PSA samples were analyzed in one laboratory with the use of the same assay, and a sample was always obtained before prostate biopsy. The method used to measure postoperative PSA levels was at the discretion of the treating physician.

FOLLOW-UP

The median follow-up was 5.1 years (range, 0.5 to 13.1), and follow-up started on the day of radical prostatectomy and concluded on September 1, 2003, or the date of death, whichever came first; no patient was lost to follow-up. Before disease recurrence, as defined by two consecutive detectable PSA values (more than 0.2 ng per milliliter) after radical prostatectomy, men generally had a serum PSA measurement every six months and an annual digital rectal examination. After a recurrence, PSA was measured a median of every 4 months (range, 1 to

12). At the time of a recurrence, biopsy of the anastomosis was not routinely performed. Overall, there were 366 recurrences and 84 deaths, 27 of which were from prostate cancer. If PSA was always detectable after radical prostatectomy, the time of recurrence was defined as time zero. Postoperative PSA data were not available for 32 men who were alive at the end of the study. Determination of the cause of death was made from death certificates in all cases. To record a death as being due to prostate cancer, there had to be documented hormone-refractory metastatic prostate cancer and evidence that the PSA level was rising at the time of the last follow-up visit before death.

STATISTICAL ANALYSIS

Calculation of the PSA Velocity

Using the PSA measurement closest in time before diagnosis (median, 1 month; range, 0.25 to 2) and all prior PSA values that had been obtained within one year before diagnosis, we used linear-regression analysis to calculate the PSA velocity during the year before diagnosis.¹²

Selection of the PSA Velocity for Study

The distribution of the time to recurrence and death from any cause was estimated according to the Kaplan–Meier method,¹³ and death from prostate cancer was estimated with the use of a cumulative incidence method¹⁴ and stratified on the basis of the 25th, 50th, and 75th quartiles for the PSA velocity during the year before diagnosis. Pairwise P values for the comparison of the distribution of the time to recurrence, death from prostate cancer, and death from any cause were calculated after adjustment for multiple comparisons with the use of a Bonferroni correction (i.e., a significant P value=0.05 divided by the number of comparisons). These P values were used to determine a cutoff point for the PSA velocity that provided the best stratification of the time to recurrence, death from prostate cancer, and death from any cause after radical prostatectomy, which was then used in the Mantel–Haenszel chi-square tests and Cox regression analyses.¹²

Pathological End Points

A Mantel–Haenszel chi-square test was used to determine whether there was a significant association between the categories of the final pathological lymph-node status (positive or negative), advancing stage on prostatectomy (T1 or T2, T3a, or T3b or T3c), Gleason score of the prostatectomy speci-

men (6 or less, 7, or 8 to 10), and the categories of annual PSA velocity (more than 2.0 ng per milliliter or 2.0 ng per milliliter or less). Cox regression analyses¹² were used to determine whether the PSA velocity during the year before diagnosis, the preoperative PSA level, the Gleason score of the biopsy specimen, and the clinical tumor stage as determined by the digital rectal examination were predictors of the time to recurrence, death from prostate cancer, and death from any cause after radical prostatectomy. In addition, a Cox regression analysis was used to test whether the PSA velocity during the year before diagnosis, final pathological lymph-node status, Gleason score on prostatectomy, margin status, and postoperative clinical tumor stage were associated with the time to death from prostate cancer and death from any cause after radical prostatectomy.

For the purpose of the Cox analyses, the PSA velocity during the year before diagnosis was considered as a categorical variable, the preoperative PSA was considered as a continuous variable, the Gleason score of the biopsy specimen (6 or less, 7, or 8 to 10), and the clinical tumor stage according to the digital rectal examination (T2 or T1c) were considered as categorical variables. The tumor stage determined on prostatectomy (T2, T3a, or T3b or T3c), Gleason score on prostatectomy (7 or less or 8 to 10), margin status, and lymph-node status were treated as categorical variables (positive vs. negative). For all categorical variables except the PSA velocity, the cutoff points were selected before the data were examined.

For all regression analyses, the assumptions of the Cox model were tested and met and all statistical tests were two-sided. This study is the first analysis of these data with respect to PSA velocity. The relative risk and 95 percent confidence intervals were calculated from the Cox model for all significant predictors of the time to recurrence, death from prostate cancer, and death from any cause after radical prostatectomy. Estimates of the time to recurrence and death from any cause with associated 95 percent confidence intervals were made according to the Kaplan–Meier method.¹³ Estimates of the time to death from prostate cancer with associated 95 percent confidence intervals were made according to the cumulative incidence method.¹⁴ For the analysis of recurrence, data were censored at the time of recurrence or, in the absence of recurrence, on the date of the last follow-up visit. No deaths occurred before recurrence.

RESULTS

SELECTING THE PSA VELOCITY FOR STUDY

Figure 1 shows the distribution of the time to recurrence, the cumulative incidence of death from prostate cancer, and the distribution of death from any cause, stratified according to the following categories of PSA velocity: 0.50 ng per milliliter per year or less, 0.51 to 1.00 ng per milliliter per year, 1.01 to 2.00 ng per milliliter per year, and more than 2.00 ng per milliliter per year. The times to recurrence, death from prostate cancer, and death from any cause were not significantly different among the categories of an annual PSA velocity of 2.0 ng per milliliter or less. By contrast, these three end points in the category of an annual PSA velocity of more than 2.0 ng per milliliter differed significantly from those in the first three categories ($P < 0.008$, adjusted for six comparisons). Therefore, the cutoff point for the PSA velocity that provided the best stratification of these three end points was 2.0 ng per milliliter per year.

PSA VELOCITY AND PATHOLOGICAL END POINTS

An annual PSA velocity of more than 2.0 ng per milliliter was significantly associated with lymph-node metastases ($P < 0.001$), an advanced pathological stage ($P < 0.001$), and high-grade disease ($P = 0.03$). Five percent of men with an annual PSA velocity of more than 2.0 ng per milliliter had positive lymph nodes, as compared with 0.7 percent of men with an annual PSA velocity of 2.0 ng per milliliter or less. Among men with an annual PSA velocity of greater than 2.0 ng per milliliter, 70 percent had stage T2 on prostatectomy, 22 percent had stage T3a, and 8 percent had stage T3c, as compared with 75 percent, 22 percent, and 3 percent, respectively, of men with an annual PSA velocity of 2.0 ng per milliliter or less ($P < 0.001$). Among men with an annual PSA velocity of more than 2.0 ng per milliliter, 69 percent had a Gleason score of 6 or less on prostatectomy, 24 percent had a score of 7, and 7 percent had a score of 8, 9, or 10, as compared with 74 percent, 23 percent, and 3 percent, respectively, of the men with an annual PSA velocity of 2.0 ng per milliliter or less ($P = 0.03$).

ASSOCIATION OF PSA VELOCITY WITH RECURRENCE, DEATH FROM PROSTATE CANCER, AND DEATH FROM ANY CAUSE

An annual PSA velocity of more than 2.0 ng per milliliter was associated with significantly shorter times

Figure 1. Kaplan–Meier Estimates of Disease Recurrence (Panel A) and Death from Any Cause (Panel B) and the Cumulative Incidence of Death from Prostate Cancer (Panel C) after Radical Prostatectomy, According to the Quartile of PSA Velocity during the Year before Diagnosis.

Disease recurrence was defined by the finding of two consecutive detectable PSA values (more than 0.2 ng per deciliter) after radical prostatectomy. In Panel A, the log-rank test yielded the following pairwise P values: P=0.48 for the comparison of 0.50 ng per milliliter per year or less with 0.51 to 1.00 ng per milliliter per year, P=0.28 for the comparison of 0.50 ng per milliliter per year or less with 1.01 to 2.00 ng per milliliter per year, P<0.001 for the comparison of 0.50 ng per milliliter per year or less with more than 2.00 ng per milliliter per year, P<0.72 for the comparison of 0.51 to 1.00 ng per milliliter per year with 1.01 to 2.00 ng per milliliter per year, P<0.001 for the comparison of 0.51 to 1.00 ng per milliliter per year with more than 2.00 ng per milliliter per year, and P=0.002 for the comparison of 1.01 to 2.00 ng per milliliter per year with more than 2.00 ng per milliliter per year.

In Panel B, the log-rank test yielded the following pairwise P values: P=0.11 for the comparison of 0.50 ng per milliliter per year or less with 0.51 to 1.00 ng per milliliter per year, P=0.41 for the comparison of 0.50 ng per milliliter per year or less with 1.01 to 2.00 ng per milliliter per year, P<0.001 for the comparison of 0.50 ng per milliliter per year or less with more than 2.00 ng per milliliter per year, P=0.32 for the comparison of 0.51 to 1.00 ng per milliliter per year with 1.01 to 2.00 ng per milliliter per year, P<0.001 for the comparison of 0.51 to 1.00 ng per milliliter per year with more than 2.00 ng per milliliter per year, and P<0.001 for the comparison of 1.01 to 2.00 ng per milliliter per year with more than 2.00 ng per milliliter per year.

In Panel C, the log-rank test yielded the following pairwise P values: P=0.99 for the comparison of 0.50 ng per milliliter per year or less with 0.51 to 1.00 ng per milliliter per year, P=0.42 for the comparison of 0.50 ng per milliliter per year or less with 1.01 to 2.00 ng per milliliter per year, P=0.006 for the comparison of 0.50 ng per milliliter per year or less with more than 2.00 ng per milliliter per year, P=0.44 for the comparison of 0.51 to 1.00 ng per milliliter per year with 1.01 to 2.00 ng per milliliter per year, P=0.003 for the comparison of 0.51 to 1.00 ng per milliliter per year with more than 2.00 ng per milliliter per year, and P<0.008 for the comparison of 1.01 to 2.00 ng per milliliter per year with more than 2.00 ng per milliliter per year.

to recurrence, death from prostate cancer, and death from any cause than an annual PSA velocity of 2.0 ng per milliliter or less. Significant increases in the relative risk of death from prostate cancer and death from any cause were also noted among men with clinical stage T2 disease and an increased PSA level at diagnosis (Table 2). The increase in the relative risks of death from prostate cancer and death from any cause remained significant when the patholog-

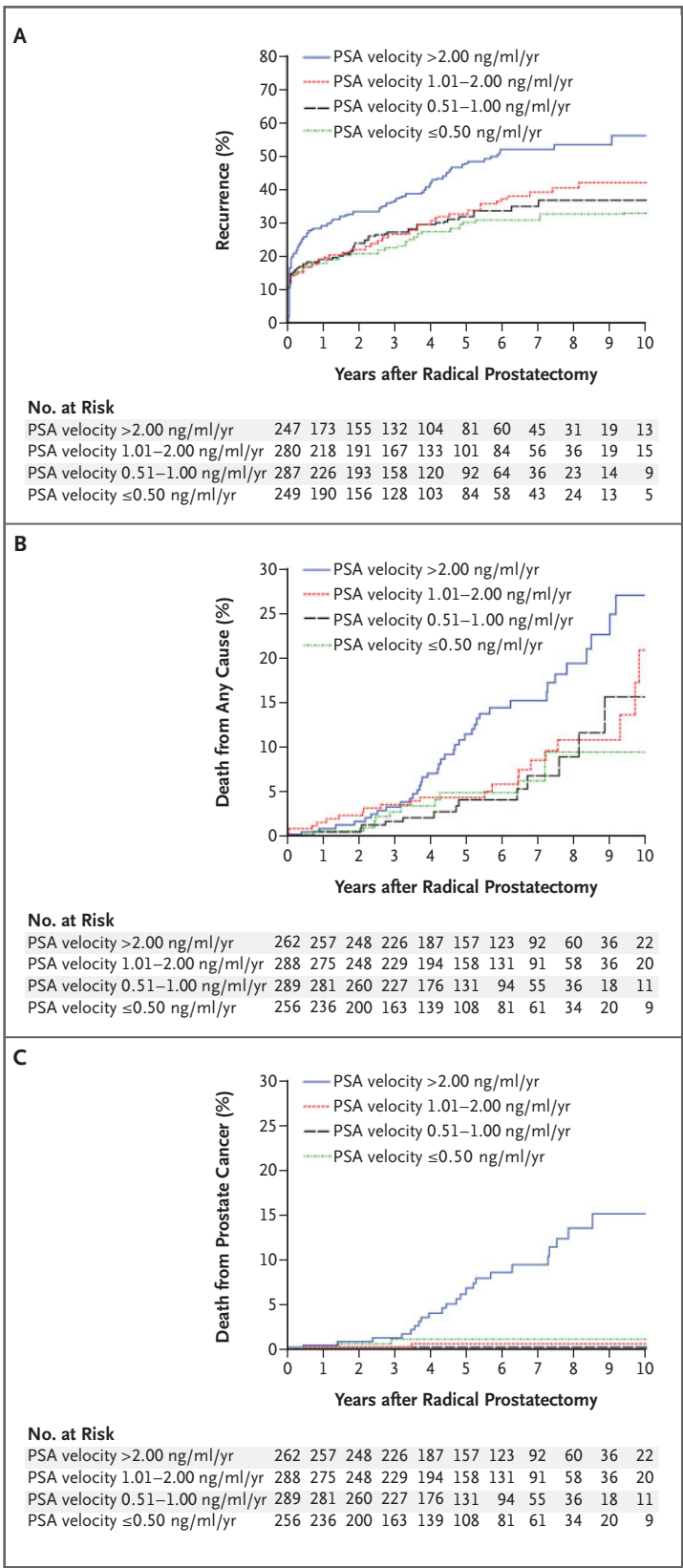


Table 2. Univariable and Multivariable Cox Regression Analyses of the Relative Risk of Recurrence, Death from Prostate Cancer, and Death from Any Cause after Radical Prostatectomy, According to the Clinical Findings at Diagnosis and the Pathological Findings at Prostatectomy.*

Covariate	No. of Men	Median Follow-up yr	No. of Events	Univariable Analysis		Multivariable Analysis	
				Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Recurrence							
PSA velocity at diagnosis							
≤2.0 ng/ml/yr	816	3.5	247	1.0†	—	1.0†	—
>2.0 ng/ml/yr	247	3.3	119	1.6 (1.3–2.1)	<0.001	1.5 (1.1–1.9)	0.003
PSA level at diagnosis (per unit increase)	1063	3.4	366	1.04 (1.02–1.06)	<0.001	1.03 (1.0–1.05)	0.008
Gleason score on biopsy							
≤6	891	3.6	292	1.0†	—	1.0†	—
7	126	2.2	49	1.4 (1.0–1.9)	0.05	1.3 (0.9–1.8)	0.10
8–10	46	2.4	25	1.9 (1.2–3.0)	0.003	1.9 (1.2–2.8)	0.006
Tumor stage at diagnosis							
1c	768	3.3	255	1.0†	—	1.0†	—
2	295	3.9	111	1.0 (0.8–1.3)	0.82	1.0 (0.8–1.3)	0.98
Death from prostate cancer							
PSA velocity at diagnosis							
≤2.0 ng/ml/yr	833	4.8	3	1.0†	—	1.0†	—
>2.0 ng/ml/yr	262	5.3	24	20.4 (6.2–67.9)	<0.001	9.8 (2.8–34.3)	<0.001
PSA level at diagnosis (per unit increase)	1095	5.1	27	1.08 (1.06–1.1)	<0.001	1.06 (1.02–1.1)	0.001
Gleason score on biopsy							
≤6	916	5.1	14	1.0†	—	1.0†	—
7	133	4.3	6	4.6 (1.7–12.2)	0.003	2.1 (0.7–5.8)	0.17
8–10	46	4.8	7	11.5 (4.2–31.4)	<0.001	3.4 (1.2–9.8)	0.02
Tumor stage at diagnosis							
1c	779	4.6	4	1.0†	—	1.0†	—
2	316	5.4	23	9.1 (3.1–26.7)	<0.001	7.4 (2.4–22.4)	<0.001
Death from any cause							
PSA velocity at diagnosis							
≤2.0 ng/ml/yr	833	4.8	45	1.0†	—	1.0†	—
>2.0 ng/ml/yr	262	5.3	39	2.6 (1.6–4.1)	<0.001	1.9 (1.2–3.2)	0.01
PSA level at diagnosis (per unit increase)	1095	5.1	84	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.06)	0.005
Gleason score on biopsy							
≤6	916	5.1	60	1.0†	—	1.0†	—
7	133	4.3	15	2.1 (1.1–3.9)	0.02	1.6 (0.8–3.0)	0.17
8–10	46	4.8	9	3.0 (1.4–6.6)	0.007	1.9 (0.9–4.4)	0.114
Tumor stage at diagnosis							
1c	779	4.6	37	1.0†	—	1.0†	—
2	316	5.4	47	2.2 (1.3–3.4)	0.001	2.0 (1.2–3.2)	0.004
Death from prostate cancer							
PSA velocity on prostatectomy							
≤2.0 ng/ml/yr	833	4.8	3	1.0†	—	1.0†	—
>2.0 ng/ml/yr	262	5.3	24	20.4 (6.2–67.9)	<0.001	12.8 (3.7–43.7)	<0.001
Gleason score on prostatectomy							
≤7	1048	5.1	18	1.0†	—	1.0†	—
8–10	47	4.8	9	13.1 (5.8–29.7)	<0.001	1.76 (0.6–5.0)	0.31

ical information available after radical prostatectomy was included in the Cox regression analyses (Table 2). The presence of lymph-node metastases, bilateral extracapsular extension, or seminal-vesicle

invasion also predicted significantly increased relative risks of death from prostate cancer and death from any cause (Table 2). On multivariable analysis, a Gleason score of 8, 9, or 10 in the prostatectomy

Table 2. (Continued.)

Covariate	No. of Men	Median Follow-up yr	No. of Events	Univariable Analysis		Multivariable Analysis	
				Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Tumor stage on prostatectomy							
2	810	5.1	8	1.0†	—	1.0†	—
3a	242	4.9	9	3.8 (1.4–9.7)	0.007	2.3 (0.6–9.7)	0.25
3b or 3c	43	4.8	10	28.2 (10.7–74.3)	<0.001	8.8 (2.4–32.6)	0.001
Nodal status on prostatectomy							
Negative	1083	5.1	22	1.0†	—	1.0†	—
Positive	12	4.4	5	24.5 (9.4–66.2)	<0.001	4.8 (1.6–14.5)	0.006
Margin status on prostatectomy							
Negative	858	5.1	12	1.0†	—	1.0†	—
Positive	237	4.9	15	4.5 (2.1–9.7)	<0.001	1.3 (0.4–4.2)	0.69
Death from any cause							
PSA velocity on prostatectomy							
≤2.0 ng/ml/yr	833	4.8	45	1.0†	—	1.0†	—
>2.0 ng/ml/yr	262	5.3	39	2.2 (1.4–3.4)	<0.001	1.8 (1.1–2.8)	0.01
Gleason score on prostatectomy							
≤7	1048	5.1	73	1.0†	—	1.0†	—
8–10	47	4.8	11	3.9 (2.1–7.4)	<0.001	1.3 (0.6–2.8)	0.58
Tumor stage on prostatectomy							
2	810	5.1	45	1.0†	—	1.0†	—
3a	242	4.9	25	1.8 (1.1–3.0)	0.015	1.2 (0.5–3.0)	0.63
3b or 3c	43	4.8	14	6.7 (3.7–12.2)	<0.001	3.9 (1.6–9.1)	0.002
Nodal status on prostatectomy							
Negative	1083	5.1	79	1.0†	—	1.0†	—
Positive	12	4.4	5	7.0 (2.8–17.2)	<0.001	3.3 (1.2–9.0)	0.017
Margin status on prostatectomy							
Negative	858	5.1	52	1.0†	—	1.0†	—
Positive	237	4.9	32	2.2 (1.4–3.5)	<0.001	1.4 (0.6–3.3)	0.39

* Recurrent disease was defined as the finding of detectable PSA levels (more than 0.2 ng per milliliter) in two consecutive serum samples after radical prostatectomy. Postoperative data on the PSA level were missing for 32 men. CI denotes confidence interval.

† This group served as the reference group in the Cox regression analysis.

samples did not by itself increase the relative risk of death from prostate cancer or death from any cause, which probably reflects the association of these scores with lymph-node metastases: 33 percent of men with Gleason scores of 8, 9, or 10 on prostatectomy had lymph-node metastases, as compared with 4 percent of men with a Gleason score of 7 or less ($P<0.001$).

DEATH FROM PROSTATE CANCER AND DEATH FROM ANY CAUSE

Figure 2 illustrates the association between the clinical tumor category, PSA level at diagnosis, and Gleason score of the biopsy specimen with the times to death from prostate cancer and death from any

cause for men with an annual PSA velocity of more than 2.0 ng per milliliter. An initial clinical stage of T2, a PSA level of more than 10.0 ng per milliliter at diagnosis, and a Gleason score of 8, 9, or 10 on needle biopsy were all associated with an increased rate of death from prostate cancer and death from any cause. Table 3 lists the contribution of the tumor stage, PSA level, and Gleason score at diagnosis to estimates of the rate of death from prostate cancer and death from any cause seven years after radical prostatectomy. Fifty percent of the patients with a PSA velocity of more than 2.0 ng per milliliter had a PSA level of 10.0 ng per milliliter or less, a clinical stage of T1c, and a Gleason score of 6 or less at diagnosis.

DISCUSSION

Previous studies⁵⁻⁷ have shown that the rate of change in PSA levels before the diagnosis of prostate cancer can predict tumor stage, grade, and in one study,⁷ the time to recurrence after radical prostatectomy. These studies were limited by the lack of a multivariate evaluation of the times to death from prostate cancer and death from any cause, after adjustment for the clinical tumor stage, the Gleason score of the needle-biopsy specimen, and the absolute serum level of PSA at diagnosis. A prior study¹⁵ found no association between the preoperative PSA velocity and the postoperative pathological findings and PSA outcomes. The study was small (consisting of 86 men), and at two years, the follow-up was relatively brief and thus may not have been adequately powerful to assess the significance of these associations. Given the evidence that disease recurrence after surgery is often not predictive of death from prostate cancer⁸ because of competing causes of mortality and the long natural history of some prostate cancers, long-term evaluation of death from prostate cancer and death from any cause is particularly pertinent.

We followed a large cohort of men for a median of more than five years and used a multivariable Cox regression analysis¹⁴ to evaluate the ability of the PSA velocity during the year before diagnosis to predict the time to death from prostate cancer, controlling for the clinical tumor stage, the Gleason score of the biopsy specimen, and the PSA level at diagnosis. Importantly, all preoperative PSA values were determined in one laboratory with the use of a single assay. The results confirmed the findings of prior investigations⁵⁻⁷ with regard to the end points of pathological stage, grade, and the time to recurrence after radical prostatectomy. They also provide new information regarding the association between the PSA velocity during the year before diagnosis and the time to death from prostate cancer or death from any cause.

Seven years after radical prostatectomy, men with an annual PSA velocity of more than 2.0 ng per milliliter before surgery had substantially higher rates of death from prostate cancer and death from any cause than men whose annual PSA velocity was 2.0 ng per milliliter or less. In addition, when a PSA velocity of more than 2.0 ng per milliliter per year was assessed in conjunction with the pathological findings at radical prostatectomy, this value remained significantly associated with the time to

Figure 2 (facing page). Kaplan–Meier Estimate of Death from Any Cause and Cumulative Incidence of Death from Prostate Cancer after Radical Prostatectomy, According to the Clinical Tumor Stage at Diagnosis (Panel A), the PSA Level at Diagnosis (Panel B), and the Gleason Score of the Biopsy Specimen (Panel C).

In Panel A, $P < 0.001$ for the comparison of clinical stage T2 with stage T1c for both death from prostate cancer and death from any cause (by the log-rank test). In Panel B, for the comparison of a PSA level of more than 10.0 ng per milliliter with one of 10.0 ng per milliliter or less, $P = 0.01$ for death from prostate cancer and $P = 0.10$ for death from any cause (by the log-rank test). In Panel C, the log-rank test yielded the following pairwise P values: for death from prostate cancer, $P = 0.06$ for the comparison of a Gleason score of 6 or less with a Gleason score of 7; $P < 0.001$ for the comparison of a Gleason score of 6 or less with a Gleason score of 8, 9, or 10; and $P = 0.10$ for the comparison of a Gleason score of 7 with a Gleason score of 8, 9, or 10; and for death from any cause, $P = 0.14$ for the comparison of a Gleason score of 6 or less with a Gleason score of 7; $P = 0.004$ for the comparison of a Gleason score of 6 or less with a Gleason score of 8, 9, or 10; and $P = 0.27$ for the comparison of a Gleason score of 7 with a Gleason score of 8, 9, or 10.

death from prostate cancer or death from any cause despite the information gained at surgery.

Our study has two clinical implications. First, men with an annual PSA velocity of more than 2.0 ng per milliliter who are otherwise healthy should consider enrolling in a randomized clinical trial in which the investigational group includes both radical prostatectomy and systemic therapy. This recommendation is based on our finding that within seven years after radical prostatectomy, depending on the clinical tumor stage, Gleason score, and PSA level at diagnosis, up to 28 percent of men with an annual PSA velocity of 2.0 ng per milliliter died of prostate cancer despite undergoing radical prostatectomy. For these men, death from prostate cancer was the leading cause of death in nearly all subgroups examined (Table 3). Second, given the relatively high rates of death from prostate cancer despite radical prostatectomy, watchful waiting may not be the best option in these men. However, we stress that whether these men would have a higher or faster rate of death from prostate cancer if they were treated with watchful waiting rather than radical prostatectomy is unknown and can only be answered by a randomized trial that compares radical prostatectomy with watchful waiting among men who received a diagnosis during the era of PSA screening.⁴

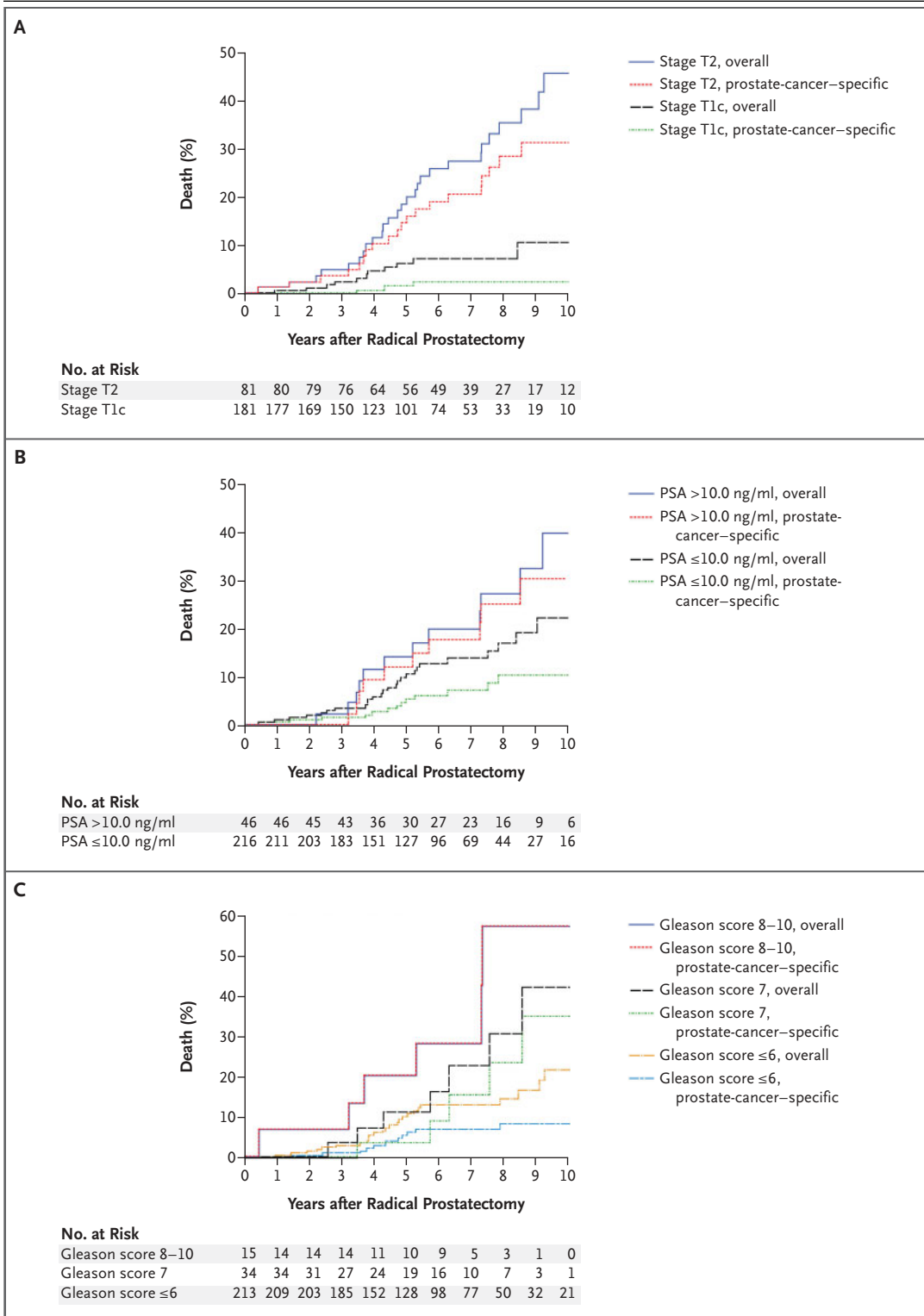


Table 3. Contribution of Deaths from Prostate Cancer to the Overall Rate of Death Seven Years after Radical Prostatectomy among Men with a PSA Velocity of More Than 2.0 ng per Milliliter per Year, According to the PSA Levels, Gleason Score, and Clinical Tumor Stage at Diagnosis.

Clinical Characteristic	No. of Men	Rate of Death	Rate of Death	Percentage
		from Prostate Cancer	from Any Cause at 7 yr	of Deaths Due to Prostate Cancer
		<i>percent (95 percent confidence interval)</i>		
All men with a PSA velocity >2.0 ng/ml/yr	262	9.2 (5.1–13.4)	15 (9.9–20.1)	61
Tumor stage at diagnosis				
1c	181	2.5 (0.1–5.3)	7.2 (2.8–11.6)	35
2a	81	20.5 (11.2–29.8)	27.4 (17.1–37.6)	75
PSA level at diagnosis				
≤10.0 ng/ml	216	7.1 (3.0–11.3)	13.8 (8.3–19.3)	51
>10.0 ng/ml	46	17.7 (5.7–29.7)	19.9 (7.4–32.4)	89
Gleason score at diagnosis				
≤6	213	6.9 (2.9–10.8)	12.8 (7.6–18.1)	54
7	34	15.4 (0.1–31.9)	22.7 (4.5–41.1)	68
8–10	15	28 (4.5–51.5)	28 (4.5–51.5)	100

Some aspects of this investigation need clarification. First, we found that an annual PSA velocity of more than 2.0 ng per milliliter was associated with a significantly increased risk of death from prostate cancer or death from any cause despite radical prostatectomy. However, the initial Gleason score, clinical tumor stage, and PSA level at diagnosis are also important determinants of the risk of death from prostate cancer. Second, although the relative risk of death from prostate cancer was nearly 10 times as high among men with an annual PSA velocity of more than 2.0 ng per milliliter as among those with an annual PSA velocity of 2.0 ng per milliliter or less, the 95 percent confidence intervals

were wide. Therefore, it is not possible to discern the exact degree of increase in the risk of death from prostate cancer for an individual patient with a preoperative PSA velocity of more than 2.0 ng per milliliter per year.

In conclusion, men whose PSA level increases by more than 2.0 ng per milliliter during the year before the diagnosis of prostate cancer may have a high risk of dying from prostate cancer despite undergoing radical prostatectomy. For these men, who are otherwise in good health, watchful waiting may not be the best option. Randomized clinical trials are needed to identify a treatment that improves survival among these men.

REFERENCES

1. Kessler B, Albertsen P. The natural history of prostate cancer. *Urol Clin North Am* 2003;30:219-26.
2. Holmberg L, Bill-Axelsson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med* 2002;347:781-9.
3. Miller DC, Hafez KS, Stewart A, Montie JE, Wei JT. Prostate carcinoma presentation, diagnosis, and staging: an update from the National Cancer Data Base. *Cancer* 2003;98:1169-78.
4. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial (PIVOT). *Oncology* 1997;11:1133-9.
5. Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992;267:2215-20.
6. Goluboff ET, Heitjan DF, DeVries GM, Katz AE, Benson MC, Olsson CA. Pretreatment prostate specific antigen doubling times: use in patients before radical prostatectomy. *J Urol* 1997;158:1876-8.
7. Egawa S, Arai Y, Tobisu K, et al. Use of pretreatment prostate-specific antigen doubling time to predict outcome after radical prostatectomy. *Prostate Cancer Prostatic Dis* 2000;3:269-74.
8. D'Amico AV, Moul JW, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate marker for prostate cancer-specific mortality following radical prostatectomy or radiation therapy. *J Natl Cancer Inst* 2003;95:1376-83.
9. Gleason DF, Veterans Administration Cooperative Urological Research Group. Histologic grading and staging of prostatic carcinoma. In: Tannenbaum M, ed. *Urolog-*

- ic pathology: the prostate. Philadelphia: Lea & Febiger, 1977:171-87.
10. Greene FL, Page DL, Fleming ID, et al. Manual for staging cancer. 6th ed. New York: Springer-Verlag, 2002:309-13.
11. Beahrs OH, Henson DE, Hutter RVP. Manual for staging cancer. 4th ed. Philadelphia: Lippincott, 1992:181-3.
12. Klein JP, Moeschberger ML, eds. Survival analysis: techniques for censored and truncated data. New York: Springer, 1997: 96-100, 229-68.
13. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
14. Gaynor JJ, Feur EJ, Tan CC, et al. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. *J Am Stat Assoc* 1993;88: 400-9.
15. Freedland SJ, Dorey F, Aronson WJ. Preoperative PSA velocity and doubling time do not predict adverse pathologic features or biochemical recurrence after radical prostatectomy. *Urology* 2001;57:476-80.

Copyright © 2004 Massachusetts Medical Society.